CORRESPONDENCE

Outcome of Cyclosporine Monotherapy in Patients of Aplastic Anemia: Experience of a Tertiary Care Hospital in Eastern India

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Received: 1 December 2015 / Accepted: 9 July 2016 / Published online: 19 July 2016
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Abstract

Introduction Immune suppression is a crucial pillar for treatment of aplastic anemia. Cyclosporine monotherapy is an easily available, affordable therapeutic option with good safety profile.

Methods and Materials This prospective study was conducted over a period of 2 years from June 2012 to July 2014. The diagnosis and response to treatment of aplastic anemia was established as per published criteria. Follow up was done at 3 and 6 months in order to assess the response. **Results** 57 patients of acquired aplastic anemia with median age of 37 years (6 to 81 years) were included in the study. 35 (62 %) cases were severe aplastic anemia, 16 (28 %) non severe aplastic anemia and 6 (10 %) were very severe aplastic anemia. At 3 months overall response rate (OR) was 7 (14 %) and at 6 months the OR rate of 11 (19.6 %) was achieved. Transiently raised creatinine, liver function abnormality and gum hypertrophy were the main side effects observed in this cohort.

Conclusion Oral cyclosporine monotherapy at dose of 5 mg/kg/day is a relatively safe treatment option for resource poor patients with aplastic anemia.

Keywords Aplastic anemia · Cyclosporine monotherapy · Response assessment

Dear Editor,

Most cases of acquired aplastic anemia is pathophysiologically characterized by T cell-mediated destruction of

bone marrow hematopoietic cells [1]. In a study by Gluckman et al. [2], cyclosporine was as effective as anti-thymocyte globulin (ATG) in patients with severe aplastic anemia (SAA). Compared to ATG, cyclosporine is less expensive, administered orally on an outpatient basis, readily available and less toxic. These advantages make it suitable for use as initial treatment for patients in developing countries, particularly since most patients cannot afford the cost of ATG. The study was intended to assess the response of oral cyclosporine at 3 and 6 months respectively.

Total 57 patients who attended hematology outpatient department of Nilratan Sircar Medical College, Kolkata from June 2012 to June 2014 were evaluated. Patients were classified as very severe, severe, non severe aplastic anemia as per Camitta criteria [3]. Viral markers for HIV, HBsAg, and HCV were negative in all patients. Oral cyclosporine was administered at dosage of 5 mg/kg in two divided doses and patients were assessed at 3 and 6 months for response [4]. Patients evaluated twice weekly during the first month and then weekly during the next month and then every 15 days a month or as indicated by the hematological or clinical status. The complete blood count, liver function tests, renal function tests, complications, side effects, number of transfusions, infections, and concomitant treatment were recorded regularly. Response assessment was done as per Camitta (2000) criteria [5]. As shown in Table 1, there were 22 (39 %) females and 35 (61 %) males in this study and median age of patients was 42 years (range: 9–77 years). The most common presentation was symptoms and signs due to anemia (97.6 %) followed by bleeding (48.4 %) and fever (21.6 %). Mean hemoglobin level was 68 g/L (range: 20–140 g/L); mean total leucocyte count (TLC) was 1100/μL (range: 200–4800/μL); mean platelet count was 8000/μL (range: 1000–100,100/

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Table 1 Clinical and laboratory characteristics of the patients (n = 57; male, 35 and female, 22)

Characteristics	Results
Median age (years)	42 (range: 9–77)
Anemia, No. (%)	55 (97.6)
Bleeding, No. (%)	27 (48.4)
Fever, No. (%)	12 (21.6)
Mean hemoglobin level (g/L)	68 (range: 20–100)
Mean total leukocyte count (per μL)	1100 (range: 200–4800)
Mean absolute neutrophil count (per μL)	386 (range: 140–750)
Mean platelet count (per μL)	8000 (range: 1000–100,000)

Fig. 1 Distribution of patients (%) according to severity of aplastic anemia (n = 57)

μL). As depicted in Fig. 1, six (11 %) patients had very severe AA, 35 (61 %) severe AA and 16 (28 %) had non severe AA. As shown in Fig. 2, at 3 months 6 (12 %) patients had partial response (PR) and 1 (2 %) had complete response (CR) with an Overall response (OR) of 7 (14 %). At 6 months, 3 (5 %) had CR, 8 (14 %) PR and 46 (81 %) had NR and OR of 19 % was achieved. There was no significant life threatening adverse events. However, as shown in Fig. 3, liver function test (LFT) abnormality was seen in 4 (7 %) patients predominantly in the form of raised total bilirubin level >2 mg/dl, alanine aminotransferase and aspartate aminotransferase level three times the upper limit of normal. Cyclosporine withheld and LFT monitored twice weekly; Cyclosporine restarted after normalization of LFT at 2.5 mg/kg/day orally for a week and gradually escalated to 5 mg/kg/day oral dose from consecutive weeks. Renal function test (RFT) abnormality was seen in only 2 (4 %) patients with raised urea and

Fig. 2 Overall response at 3 and 6 months (n = 57)

creatinine level. Serum creatinine level was >2 mg/dl with satisfactory urine output. Urine analysis was normal, treated with supportive care with no requirement for hemodialysis. Cyclosporine withheld temporarily; serum creatinine monitored twice weekly until it returned to baseline. In both the patients, creatinine level reached normal after 3 weeks of drug discontinuation; restarted with cyclosporine 3 mg/kg/day after close monitoring of creatinine level. It was gradually escalated to 5 mg/kg/day with no further elevation in the creatinine level. Gum hypertrophy was seen in 5 (9 %) patients, cyclosporine continued with gradual spontaneous recovery.

Most patients of AA coming to our OPD belong to lower socio-economic status and in a study from India it was seen AA is common in lower socioeconomic status [6]. Most

Fig. 3 Distribution of patients (%) showing gum hypertrophy, liver function and renal function abnormality (n = 57)

patients could not afford the cost of allogenic stem cell transplant or ATG therapy. In a very recent study from eastern India, among all causes of pancytopenia, aplastic anemia was the commonest [7]. Among our study population there is male preponderance and median age is in early fourth decade similar to other study from India. Most common presentation was anemia followed by bleeding disorder which is similar to study by Chakrabarti et al. [7, 8]. Most of our AA patients were having severe in 35 (61 %) cases and very severe in 6 (11 %) cases. At 3 months, OR was 7 (14 %) with 6 (12 %) PR and one

(2 %) CR was achieved. Gluckman et al. [2] had shown CR + PR response rate of 16 % at 3 months. At 6 months, OR, CR and PR was achieved in 11 (19 %), 3 (6 %), 8 (14 %) cases respectively. Study by Marsh et al. [4] have shown overall response rate of 46 % at 6 months. The difference in OR at 6 months in comparison to other studies was possibly due to the fact that most of our patients were having severe and very severe aplastic anemia, most of them were farmers and pesticide exposure may be the cause of aplastic anaemia [8]. With long term cyclosporine therapy, LFT abnormality was commonest; 4 (7 %) with transient elevation of liver enzymes and bilirubin level which responded to temporary discontinuation of cyclosporine. Classical gum hypertrophy was seen in 5 (9 %) of our patients. Cyclosporine was not withheld for gum hypertrophy, we advised proper oral hygiene and none of our patients on follow up showed further complications or progression. Tokuda et al. [9] reported gum hypertrophy in 10 % of patients with SLE using low dose cyclosporine. Renal abnormality in the form of raised serum creatinine level was seen in only 2 (4 %) of our patients and it responded to temporary discontinuation of cyclosporine. The only limitation of our study was that therapeutic monitoring of cyclosporine was not done due to financial constraints but a study from Iran in renal transplant setting had shown that monitoring trough level of cyclosporine has no direct relationship with side effect [10]. To conclude, cyclosporine monotherapy is good therapeutic option in patients of aplastic anemia in a resource driven country like India. However, the response rate at 6 months is modest. Cyclosporine monotherapy is well tolerated by majority of the patients.

Authors Contribution

Contributor	Concept	Study design	Data collection	Statistical analysis	Literature overview	Discussion	Fund generation
Prakas Kumar Mandal	Yes	Yes	Yes	Yes	Yes	Yes	Nil
Suvraneel Baul	Yes	Yes	Yes	Yes	Yes	Yes	Nil
Tuphan Kanti Dolai	Yes	Yes	–	–	–	Yes	Nil
Rajib De	Yes	Yes	–	–	–	Yes	Nil
Prantar Chakrabarti	Yes	Yes	–	–	Yes	Yes	Nil

Compliance with Ethical Standards

Conflict of interest The authors have declared no competing interests.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee.

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